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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,321	CHARLES ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 11-26* is/are pending in the application.

4a) Of the above claim(s) *15-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11-14 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 3 September 2002 as the US national stage of international application PCT/GB00/02924 filed 28 July 2000, which claims benefit of foreign patent applications GB 9918076.2, filed 30 July 1999, and GB 0016172.9, filed 30 June 2000. The preliminary amendment filed 11 February 2002 has been entered. Claims 1-26 were originally filed. Claims 3-5, 11-14, 19-23, 25 and 26 were amended and claims 8-10 were canceled in the 11 February Paper. Claims 1-7 and 11-26 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-7, 11-14 and 26) in the reply filed on 18 May 2004 is acknowledged.

Claims 15-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention. Claims 1-7, 11-14 and 26 are presently under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 30 June 1999. It is noted, however, that applicant has not filed a certified copy of the GB 0016172.9 application as required by 35 U.S.C. 119(b).

Sequence Compliance

Applicant's submission of a Paper copy and computer readable form of the sequence listing with the Paper filed 21 October 2001 is acknowledged. However, the "STATEMENT PURSUANT TO 37 CFR 1.823(b)" filed with the sequence listing does not fulfill the requirement of Rule 1.825(b) which states, "Amendments must also be accompanied by a statement that indicates support for the amendment in the application, as filed, and a statement that the replacement compact disc includes no new matter." A response to this Office Action should include the proper statement according to 37 CFR 1.825(b).

Claim Objections

Claims 5 and 26 are objected to because of the following informalities: Claim 5 is objected to because the phrase "which are the microcapsules are" in line 1 is grammatically incorrect.

Claim 26 is objected to as depending from a nonelected base claim. Claim 26 should be amended such that the limitations of the claims from which it depends are recited in the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 11-14 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims are directed to microcapsules, methods of making microcapsules and methods of using microcapsules wherein said microcapsules harbor cells containing a polynucleotide comprising a coding sequence for a nitric oxide synthase or a functional variant thereof.

The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 1, page 1105).

In the instant case, the "polynucleotide comprising a coding sequence for a nitric oxide synthase or a functional variant thereof" is a critical element of the claimed invention because it is required for the utilities asserted for the claimed invention, *i.e.*, treatment of conditions which are associated with deficient NO production or manufacture of a medicament for the use in

treatment of a condition associated with deficient NO production (first full paragraph on page 23).

A "functional variant" of a NOS is defined in the third full paragraph on page 10 of the specification as "any polypeptide which demonstrates NOS activity". Although "NOS activity" itself is not explicitly defined, the broadest reasonable interpretation of the phrase is any polypeptide capable of synthesizing nitric oxide. Thus, the polynucleotide encoding a sequence for a functional variant of NOS of the claims is understood to be generic to a polynucleotide encoding any polypeptide capable of synthesizing nitric oxide.

Although a family of enzymes capable of producing nitric oxide from arginine via the reaction mechanism L-arginine +NADPH+O_2→citrulline + nitric oxide + $NADP^+$ is well characterized and conventional in the art (see, *e.g.*, Ghosh *et al.* (2003) *Front. Biosci.* 8: 193-209), the art does not generally describe "any polypeptide which demonstrates NOS activity".

The specification teaches that functional variants of a NOS may be a fragments of a full length NOS or structurally related to a naturally occurring NOS (page 10, lines 24-30). However, the functional variant is not limited to being structurally related to a conventional NOS in any way and the specification fails to set forth the relevant identifying characteristics of a polypeptide which demonstrates NOS activity beyond reference to what is conventional in the art. Thus, the specification fails to provide adequate written description for any polypeptide which demonstrates NOS activity

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for

the broad class of functional variants of a NOS. Therefore, only the conventional iNOS, nNOS and eNOS enzymes meet the written description provision of 35 U.S.C. §112, first paragraph.

With respect to the method claims, adequate description of the methods first requires an adequate description of the materials which provide the means for practicing the invention.

Claims 1-7, 11-14 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to microcapsules suitable for administration to a human or animal wherein said microcapsules harbor cells containing a polynucleotide construct comprising a nitric oxide synthase coding sequence operably linked to a tetracycline or ecdysone inducible promoter, a pharmaceutical composition comprising said microcapsules, a method of delivering said microcapsules to a host,

a method of treating a host suffering from a condition associated with deficient NO production comprising administering said microcapsules and a method of making said microcapsules.

With regard to using the claimed microcapsules and compositions or preparations comprising said microcapsules, the specification teaches that the microcapsules may be used to treat conditions which are associated with NO production, which are defined as including those that may be a result of abnormal deficient NO production and also those that although not a result of abnormal NO production as such, may be treated by raising NO levels. In particular, the specification teaches that the microcapsules can be used to treat hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure or schizophrenia (second paragraph on page 23). The specification further teaches that the microcapsules may be used as artificial macrophages in the treatment of cancers (third paragraph on page 23).

As the enabling disclosure must teach the skilled artisan how to make *and* use the claimed invention, and the only asserted utility for the invention is as a therapeutic, it is incumbent upon the specification to set forth manner and process of using the disclosed microcapsules as therapeutics, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected to use the invention as a therapeutic in the treatment of hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure, schizophrenia or cancer.

State of the prior art and level of predictability in the art: The relevant art provides no guidance regarding how to use microencapsulated cells genetically modified to express a nitric

oxide synthase under the control of an inducible promoter to treat any condition. However, the art does teach that the therapeutic use of encapsulated cells in general remains at an early stage of development. In a review of the art published 4 years after the effective filing date of the instant application, Orive *et al.* (2003) *Nat. Med.* 9:104-107, teaches, "[d]espite considerable interest, however, the field [of cell encapsulation] has not lived up to expectations. A lack of reproducibility, or uncertainty surrounding the reproducibility of prior studies has been a major problem" (second paragraph on page 104). Orive *et al.* cites several examples of promising studies that could not be reproduced and suggests a number of problems that must be addressed in the development of clinical applications of encapsulated cells. In the paragraph bridging the right and left columns on page 104, Orive *et al.* teaches, "[t]echnological and biological limitations...must be overcome if the promise of cell encapsulation is to be realized. Some of the important considerations for consistent clinical success of cell encapsulation include a source of functional cells; a biocompatible, as well as mechanically and chemically stable membrane of a suitable permeability cut-off value that provide immune protection to the implant; functional performance; biosafety; and long-term survival of the graft." Orive *et al.* goes on to specifically identify assessment of dosage and transplantation site (*i.e.*, route of administration) as important considerations as challenges to be addressed (first full paragraph on page 105 and the paragraph bridging the left and right columns on page 105). Finally, in remarking on the future of cell microencapsulation as a viable therapeutic approach, Orive *et al.* states, "[c]ell microencapsulation is a technology with enormous clinical potential for the treatment of a wide range of diseases. Yet many difficulties remain, some of which will certainly challenge our scientific ingenuity. The stepwise analysis of the essential obstacles, coupled with increased

international collaboration, should move the technology forward in a careful and controlled way and bring it much closer to clinical reality" (final paragraph on page 106).

Taken together, the teachings of Orive *et al.* demonstrate that, even four years after the effective filing date of the instant claims, therapeutic application of microencapsulated cells was yet to become a clinical reality, reproducibility of promising findings was unpredictable and many challenging difficulties remained to be overcome before the therapeutic application of microencapsulated cells would be enabled.

With regard to therapeutic application of encapsulated cells inducibly expressing a nitric oxide synthase to conditions such as hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure or schizophrenia, the art suggests challenges beyond those common to all microencapsulation strategies. First, NO is known to have an extremely short half-life *in vivo*. For example, Kelm (1999) *Biochim. Biophys. Acta* 1411: 273-289 teaches that the half-life of NO in blood has been estimated at 0.05-1.8 ms (see especially the first full paragraph on page 278) and Murphy (1999) *Biochim. Biophys. Acta* 1411:401-414 teaches that NO produced *in vivo* diffuses only several cell diameters (paragraph bridging the left and right columns on page 402). Consequently, Murphy *et al.* teaches, the steady state NO concentration experienced by a cell is determined by the number of NO-producing cells nearby. Thus, Kelm and Murphy teach that NO is a paracrine messenger effective only over distances of several cell diameters *in vivo*. Therefore, absent evidence to the contrary, the skilled artisan would expect that effective administration of the instant microcapsules would require that they be no more than a few cell diameters from the target cell in sufficient quantity to provide the desired effect.

In addition to the short half-life and limited range of NO, Murphy points out another complication in developing a therapeutic strategy using the instant claimed invention, which is the potent cytotoxicity of NO. Murphy teaches that increased concentrations of NO lead to formation of highly reactive $ONOO^-$ leading to oxidative damage of a wide range of biological molecules, including proteins, lipids and nucleic acids (see especially the paragraph bridging the left and right columns on page 403). Thus, the skilled artisan would understand that the production of NO must be carefully controlled in order to provide a therapeutic effect in chronic conditions such as hyperlipidemia, renal failure, hypertension, restenosis, atherosclerosis, heart failure or schizophrenia without generating toxic concentrations of NO and $ONOO^-$ leading to damage to the host cells or to the engrafted cells such that the therapy fails.

Thus, the enabling disclosure should teach the skilled artisan the proper dosage and mode of administration to achieve therapeutic effect in the treatment of hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure, schizophrenia, or cancer in light of the extremely short half-life and limited range of NO *in vivo* and the pronounced toxicity of NO when produced in excessive quantity.

As the present invention is based on recombinant gene expression, additional art-recognized complications to achieving a therapeutic effect using the instant encapsulated cells are apparent from the gene therapy art. In particular, has been recognized for many years that identifying effective promoters for therapeutic use is problematic. For example, Verma *et al.* (1997) *Nature* 389: 239-242 teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved and warns, "the search for such

combinations is a case of trial and error for a given type of cell" (page 240, paragraph bridging columns 2-3). With particular regard to the inducible promoter systems used in the instant invention, the art teaches that, at the time of filing, therapeutic use of the promoters remained under investigation and was not considered enabled. For example, Graham (2002) *Expert Opin. Biol. Ther.* 2:525-535 teaches, "[w]hile the initial indications are promising, the toxic, carcinogenic and teratogenic potential of ecdysteroids and other EcR agonists intended for clinical use as transgene inducers obviously require more thorough investigation, and this becomes especially necessary if prolonged exposure is envisaged" (first full paragraph on 532) and "[t]he recombinant expression of EcR in mammalian cells, often in conjunction with rRXR overexpression, may have unintended-and as yet undiscovered-effects on host cell physiology" (paragraph bridging the left and right columns on page 532). Agha-Mohammadi *et al.* (2000) *J. Clin. Invest.* 105:1177-1183 teaches that the level of transgene expression obtained using the tetracycline-regulatable system (TRS) was extremely variable, reflecting "the many poorly controllable aspects of these systems, including the cell type, the surrounding context of vector/integration site, and the basal intracellular concentration of transgene" (first full paragraph on page 1182). Agha-Mohammadi *et al.* further teaches, "most of the reported vectors have shown relatively high basal expression and therefore limited efficiency of the system" and in spite of recent improvements in induction of expression "still more efficient regulatory systems will be necessary to achieve regulated gene expression *in vivo*" (second full paragraph on page 1182).

Thus, the relevant art teaches that at the time of filing achieving sustained gene expression *in vivo* was generally problematic, and therapeutic application of inducible promoters

was not routine in the art. In particular, the art teaches that tight control of inducible promoters remained difficult, adding to the unpredictability of establishing a therapeutic protocol using the claimed invention in light of the potentially narrow therapeutic index of the invention (*Id.*).

Finally, with regard to application of the invention to the treatment of cancer, the art teaches that the development of such therapies is confounded by the lack of predictive models for the treatment of human cancers. In particular, the art teaches that xenograft cancer models are poor predictors of clinical efficacy. For example, Gromeier *et al.* (2001) *Curr. Opin. Mol. Ther.* 3:503-508 states, "[a]ll too often, the antitumor effects of oncolytic agents evident in established cell lines have been extrapolated to all tumors represented by the chosen cell line. Many tumor cell lines, although indispensable for orientating investigations, are very poor representations of the original tumors" (paragraph bridging pages 506-507). The position of Gromeier *et al.* is supported by the fact that, as pointed out by Gura (1997) *Science* 278: 1041-1042, "since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the U.S. Food and Drug Administration" (second paragraph in the left column on page 1041). Gura further states, "[p]harmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs" (third paragraph in the left column on page 1 041). These statistics led Alan Oliff, executive director for cancer research at Merck Research Laboratories to

conclude, "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (Gura, page 1041, second paragraph in the left column).

Thus, the art recognized that even very promising results obtained with xenotransplantation models of human cancer seldom translated into the clinic. Therefore, establishing a therapeutic method for the treatment of cancer, even in light of success in animal models, was unpredictable at the time of filing.

Amount of direction provided by the inventor and existence of working examples: With regard to the therapeutic application of the instant microencapsulated cells to the treatment of hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure and schizophrenia the instant disclosure provides no working examples in spite of the extraordinarily disparate nature of the diseases to be treated.

The working examples do describe establishment of a cell lines expressing iNOS under the control of an ecdysone- or tetracycline-inducible promoter and encapsulation of one of the cell lines in alginate. The encapsulated cells were demonstrated capable of surviving 8 days *in vitro* (Example 4; Figure 5) and two days *in vivo* (Example 5). In Example 6, the specification teaches that when the encapsulated cells are admixed with a tumor cell line and stimulated with inducing agent *in vitro*, the *in vivo* tumorigenicity of the tumor cells is reduced. However, this approach to treating cancer is not art recognized as a model of cancer therapy and the skilled artisan would not consider the experiment as a working example of *in vivo* cancer therapy. Thus, the disclosure provides no working examples of the only contemplated utility for the claimed invention (*i.e.*, therapy).

With regard to clinical application of microencapsulated cells, the specification provides only general teachings which were readily available to the skilled artisan at the time of filing (see especially the section entitled "Microcapsules" beginning on page 15). In view of the teachings of Orive *et al.*, which demonstrate that even four years after the effective filing date of the instant claims, therapeutic application of microencapsulated cells was yet to become a clinical reality, the skilled artisan would not expect to be able to use the claimed encapsulated cells to treat any disease without additional experimentation.

Likewise, teachings directed to dosage and route of administration are limited to generalizations and the assertion that "the dose of microcapsules may be determined according to various parameters, especially according to the microcapsules used; the age, weight and condition of the patient to be treated; the route of administration; the required regimen; and the condition to be treated" (second full paragraph on page 25). The teachings in the specification do not even contemplate the particularly challenging aspects of the instant invention (*i.e.*, the short half-life, limited range and pronounced toxicity of NO, and the art recognized difficulties of therapeutic application of ecdysone- or tetracycline-inducible promoters) and therefore place a particularly large burden on one of ordinary skill seeking to use the invention.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the relevant art is high, the ordinary skilled artisan would not be able to use the instant claimed invention without engaging in undue experimentation. As noted above, neither the disclosure nor the relevant art provide a single working example of a therapeutic use for the claimed invention or even a closely related invention. Although, the specification need not contain an example if the invention is otherwise

disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

In the instant case, the specification clearly does not disclose the manner and process of using microencapsulated cells comprising a construct in which a NOS is operably linked to an ecdysone- or tetracycline-inducible promoter to treat any condition. The art teaches that the platform technologies upon which the invention is based (*i.e.*, microencapsulated cells, and tetracycline- and ecdysone-inducible promoters) were not enabled for clinical use at the time of filing or well after the time of filing. Given that the specification provides no guidance regarding microencapsulation or inducible promoters beyond what was readily available in the art, the skilled artisan seeking to use the invention as contemplated in the specification would clearly have to engage in undue experimentation to enable the platform technologies.

Furthermore, even if the platform technologies were enabled for clinical use, developing a therapeutically effective strategy to treat any given condition would require undue experimentation. The specification provides no specific guidance at all with regard to how one should administer the encapsulated cells to treat of hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure or schizophrenia. Given the volatile nature of NO *in vivo* the skilled artisan would expect that the encapsulated cells would have to be administered such that they are in close proximity to the relevant target cell; however, the specification provides no guidance as to what the relevant target cells would be or how to deliver the microcapsules to those particular cells. Furthermore,

given the toxicity of NO, the skilled artisan would expect that NO expression would have to be tightly regulated in order to achieve a therapeutic effect without inducing toxicity in the patient or in the engrafted cells.

Likewise, the skilled artisan seeking to treat cancer using the microencapsulated cells would not know how to treat a clinically relevant tumor *in situ* using the invention. The admixture of dispersed tumor cells with dispersed microencapsulated cells as provided in Example 6 clearly fails to model the complexity of a tumor *in situ*, and given the general failure of xenograft tumor models of cancer to predict clinical efficacy of cancer treatments, the clinical outcome of administering the encapsulated cells to a cancer patient is highly unpredictable. Thus, the skilled artisan seeking to use the microencapsulated cells of the invention to treat cancer would clearly have to engage in undue experimentation to establish a clinically efficacious treatment.

Given these considerations, it is apparent that one of ordinary skill in the art would not be able to use the claimed microcapsules in a method of treating a host suffering from a condition associated with deficient NO production without undue experimentation. Thus, the specification fails to identify an enabled use for the claimed products. Furthermore, as there is no enabled use for the products, the method of making said microcapsules also lacks an enabled use. Therefore, the claims are rejected under 35 U.S.C. §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim limits the microcapsules of claim 1 to containing "an average of from 1 to 1 x 10^7 cells." The metes and bounds of the claimed subject matter are unclear because the claim does not recite a relevant unit of measure. The claim recites that the plural "microcapsules" contain an average number of cells. The meaning of the claim depends on the number of microcapsules containing the cells. For example, do the microcapsules contain an average of 10^7 cells per microcapsule, per 100 microcapsules, per 1000 microcapsules?

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636